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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/585,743	06/02/00	SEDRANI R	100-8024C/C1

001095
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EXAMINER	
CEPERLEY, M	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/585,743	Applicant(s) SEDRANI ET AL.	
	Examiner Mary E. (Molly) Ceperley	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *8-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☒ Other: *Ex parte Erlich decision* .

1. Applicants' election of Group I, claims 1-7, 13 and 14 in Paper No. 4 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 5-7, 13 and 14 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n).

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-7, 13 and 14 are rejected under 35 USC 112, second paragraph, as being indefinite for the following reasons.

a) In claim 1, it is unclear what is meant by the term "a rapamycin" since "rapamycin" is a single compound and not a class of compounds.

b) A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as

to where broad language is followed by "preferably" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 5 recites the broad recitation "a 40-O-alkylated rapamycin", and the claim also recites "preferably..." which is the narrower statement of the range/limitation.

c) The term "capable of" renders the claims indefinite. It is unclear whether the claims actually do bind to rapamycin because having the capability is not the same thing as actually performing the function. A positive recitation of the function is required.

d) Claim 4 is vague and indefinite due to the recitation of the phrase "obtainable by". Claim 4 is a product by process claim which needs to state that the product was obtained by the process.

e) Claim 6 needs to be amended to recite the conventional Markush terminology "selected from the group consisting of".

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-7, 13 and 14 are rejected under 35 USC 112, first paragraph, as containing subject matter which was dot described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification at pages 1 and 2 indicates that the production of antibodies to rapamycin is, at best, problematical:

"There have been no previous reports of monoclonal antibodies which recognize rapamycin. There are inherent difficulties in making monoclonal antibodies to rapamycin because rapamycin is not immunogenic and is itself extremely immunosuppressive."

In view of the state of the art as described by applicants, it is considered that absent a deposit in accordance with the Budapest Treaty of a hybridoma which produces the claimed rapamycin antibodies, one skilled in the art would not be able to reproducibly practice the claimed invention without undue experimentation. Applicants are further advised that to provide enabling support for the individual claims which recite ***different specificities*** for the antibodies (e.g. claim 2: "recognizing an epitope on the FKBP-binding portion"; claim 7: "capable of distinguishing between rapamycin and a 40-O-alkylated rapamycin") would require in each instance that a deposit be made of a hybridoma which produces monoclonal antibodies having the recited claimed characteristic. If an ATCC deposited hybridoma is ***not specifically claimed*** but is only used ***to support a claimed antibody specificity***, applicants will need to additionally

establish that, in addition to the monoclonal antibodies of the ATCC deposit, other monoclonal antibodies having the requisite specificity can be reproducibly prepared.

Applicants' attention is directed to *In re Lundak*, 773 F.2d. 1216; 117 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-7, 13 and 14 are rejected under 35 USC 103(a) as being obvious over each of ***(1)*** Stella et al (U.S. 4,650,803), Failli et al (A) (U.S. 5,177,203), Kao et al (U.S. 5,118,678), Kao (U.S. 5,194,447), Caufield (U.S. 5,118,677), Amer. Home Prods. (WO 92/05179), or Failli et al (B) (U.S. 5,130,307) taken in combination with each of references ***(b)*** Sevier et al (Clinical Chemistry, 27/11, 1797-1806 (1981); Yelton et al (American Scientist, 68, 510-516 (1980)); or Campbell (Monoclonal Antibody and Immunosensor Technology, Chapter 1, Elsevier (1991)).

Each of references ***(1)*** describes pharmaceutically active rapamycin derivatives which are substituted at the positions which correspond to either the 40- or 28-position of the rapamycin compounds as depicted in structure (III) of page 4 and Formula B of page 8 of the instant application. Please note that the 40-position of the rapamycin ring

may be equivalently described as the 42- position and that the 28- position may be described as the 31- position depending on the numbering system used by a given set of authors/inventors. See Stella et al: Figure 1; col. 1, lines 49-68; Failli et al (A): structure (I); Kao et al: col. 1, line 45 – col. 2, line 34; Kao: abstract; Caufield: abstract; Amer. Home Prods.: title and abstract; Failli et al (B): abstract. These references establish that rapamycin 40- or 28-substituted rapamycin derivatives are well known pharmaceutically active agents. These references do not describe the production of antibodies specific for these pharmaceutical agents.

References ***(2)*** establish that it is well known in the art that monoclonal antibodies to an extremely wide variety of known antigens may be prepared using conventional immunogenic hapten-carrier conjugates. See Sevier et al, the entire article, in particular, Table 2; Yelton et al: the entire article; Campbell: the entire article, in particular, section 1.17.6.

Given the fact that 40- and 28- substituted rapamycin derivatives are well known drugs (references ***(1)***), it is considered to be well within the level of skill in the art and therefore obvious to substitute these derivatives as haptens in a conventional method of preparing immunogenic conjugates as described in references ***(2)***, as claimed, with the expectation of conventionally using these immunogens to obtain similarly useful antibodies specific for rapamycin and its derivatives. See *Ex parte Erlich,* 3 USPQ2d 1011, in particular, page 1015, column 1.

The features of the dependent claims are either specifically described by the references (e.g. the conventional preparation of monoclonal antibodies of instant claim

4) or constitute obvious variations in parameters which are routinely modified in the art (e.g. specificity of an antibody for more that one epitope) and which have not been described as critical to the practice of the invention. The packaging of reagents in kit form is an obvious expedient for ease and convenience in assay performance.

9. Claims 1-7, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of references ***(1)*** of paragraph 8. above taken in combination with each of references ***(2)*** of paragraph 8. above and further in combination with Niwa et al (U.S. 5,532,137).

References ***(1)*** and ***(2)*** are applied for the reason stated in paragraph 8. above.

Niwa et al is applied for its description of the preparation of immunogens which use FR-900506, a macrocyclic structure very similar to rapamycin, as a hapten. See the structure of col. 7 where the point of attachment of the linker is at a position which corresponds to the 40-position of the instant rapamycin derivative and the monoclonal antibody production of Example 2.

Given the fact that 40- and 28- substituted rapamycin derivatives are well known drugs (references ***(1)***), it is considered to be well within the level of skill in the art and therefore obvious to substitute these derivatives as haptens in a conventional method of preparing immunogenic conjugates as described in references ***(2)***, as claimed, with the expectation of conventionally using these immunogens to obtain similarly useful

antibodies specific for the 40- and 28-substituted rapamycin epitopes. This is particularly true in view of the further teaching of Niwa et al that antibodies to very structurally similar macrocyclic compounds can be prepared using 40-substituted hapten/carrier conjugates.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. (Molly) Ceperley whose telephone number is (703) 308-4239. The examiner can normally be reached from 8 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-7230.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Mary E. Ceperley

September 25, 2001

Mary E. Ceperley
Primary Examiner
Art Unit 1641